doi 10.3969/j.issn.1673-4254.2016.10.14
J South Med Univ, 2016, 36(10): 1382-1385

临床研究

肾病综合征患儿的血清游离脂肪酸与白蛋白比值显著升高

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摘要:目的 通过分析儿童肾病综合征(NS)患者血清游离脂肪酸(NEFA)和白蛋白(ALB)的水平,探讨急性期和恢复期NS患儿血清NEFA/ALB比值的变化及差异。**方法** 分别测定急性期NS患儿55例、恢复期NS患儿33例和健康对照儿童122例的血清NEFA、ALB水平,计算NEFA/ALB比值,同时分析其它血脂及肾功能参数水平。**结果** 与健康对照组相比,NS患儿血清ALB(t=11.152,P<0.001)水平显著降低,NEFA/ALB比值(t=4.991,P<0.001)显著升高;其中,急性期患儿较恢复期患儿血清ALB(Z=7.822,P<0.001)水平显著降低,NEFA/ALB比值(t=4.689,P<0.001)显著升高。相关性分析显示,NS患儿血清NEFA/ALB比值与胆固醇(r=0.564,P<0.001)、甘油三酯(r=0.444,P<0.001)、低密度脂蛋白(r=0.625,P<0.001)、尿素(r=0.437,P<0.001)、肌酐(r=0.278,P=0.013)、尿酸(r=0.397,P<0.001)水平均呈显著正相关,与总蛋白(r=-0.461,P<0.001)水平呈显著负相关。逐步多元线性回归分析显示,在校正其他相关因素的影响下,NS患儿血清NEFA/ALB比值与尿素水平呈显著独立相关(β=0.703,P=0.001;校正R^2=0.494)。**结论** 儿童NS患者血清NEFA/ALB比值显著升高,与其肾功能损伤密切相关,有望作为其临床病情评估的新指标。
关键词:肾病综合征;游离脂肪酸;白蛋白;肾功能

Serum non-esterified fatty acids to albumin ratio increased significantly in children with nephrotic syndrome

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Abstract: Objective To analyze serum levels of non-esterified fatty acids (NEFA) and albumin (ALB) in children with nephrotic syndrome (NS) and investigate the clinical significance of altered serum NEFA to ALB ratio in children with NS in acute and remission phases. **Methods** Serum levels of NEFA and ALB were measured in 55 NS children in acute phase, in 33 NS children in remission and in 122 healthy control children, and the ratio of NEFA to ALB was calculated. The other lipid/lipoprotein and renal function parameters were also analyzed in these children. **Results** Compared with the healthy control children, children with NS had a significantly decreased serum ALB level (t=11.152, P<0.001) and a significantly increased NEFA to ALB ratio (t=4.991, P<0.001). Compared with NS children in remission, those in acute phase showed a significantly decreased ALB (Z=7.822, P<0.001) and an increased NEFA to ALB ratio (t=4.991, P<0.001). In all the NS children, NEFA to ALB ratio was positively correlated with the levels of TC (r=0.564, P<0.001), TG (r=0.444, P<0.001), LDL-C (r=0.625, P<0.001), urea (r=0.437, P<0.001), creatinine (r=0.278, P=0.013), and uric acid (r=0.397, P<0.001), while negatively correlated with the level of total protein (r=-0.461, P<0.001). Multiple linear regression analyses showed that NEFA to ALB ratio was independently associated with serum urea levels (β=0.703, P=0.001; adjusted R^2=0.494) after adjustment of other related factors. **Conclusion** Serum NEFA to ALB ratio is significantly increased in NS children in close association with impaired kidney function, and may function as a novel parameter for assessing the development of NS.
Key words: nephrotic syndrome; non-esterified fatty acids; albumin; kidney function

儿童肾病综合征(nephrotic syndrome, NS)是一种常见的儿科肾脏疾病,以肾小球基膜通透性增加伴肾小球滤过率降低为病理基础,引起患者出现大量蛋白尿、低蛋白血症、高脂血症等一系列临床症状[1]。若治疗不及时,则可并发肾小管损伤,严重时可发展为慢性肾衰竭。游离脂肪酸(NEFA)是脂肪代谢的产物,在血循环中主要与白蛋白(ALB)相结合,生理状态下处在较低水平;病理性升高的NEFA具有细胞和组织毒性,可促使肾小管功能受损[2]。文献证实,在伴蛋白尿的慢性肾病中,经ALB运载的NEFA是促进肾小管损伤的重要

收稿日期:2016-02-13
基金项目:国家自然科学基金(81271904,81572074);国家重大科学仪器设备开发专项(2012YQ03026109);成都军区课题(C41007)
Supported by National Natural Science Foundation of China (81271904, 81572074).
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因素[3-5]。已发现,NS患者血浆NEFA水平变化不一,但其NEFA/ALB比值呈增高趋势[3-5]。新近研究表明[6],在NS的动物模型体内,血浆NEFA/ALB比值明显升高,并与NS的发生发展密切相关。但目前国内尚未见有关NS患儿血清NEFA水平及NEFA/ALB比值变化的研究报道,因此,本研究旨在通过分析儿童原发性NS患者的血清NEFA、ALB水平,探讨急性期和恢复期NS患儿血清NEFA/ALB比值的变化及差异,以期为临床NS患儿的病情评估提供新的指标。

1 资料和方法

1.1 临床资料

2014年3月~2014年5月在南京军区南京总医院肾内科住院的儿童原发性NS患者88例,均排除患有先天性NS、糖尿病、慢性肝病及家族性血脂异常。所有患儿均符合NS诊断标准[7],尿蛋白排泄量>50 mg/kg/d;其中急性期患儿(ALB≤30 g/L,新发且尚未接受激素治疗)55例,年龄1~15(5.60±3.56)岁;恢复期患儿(ALB>30 g/L,已接受常规激素治疗,首始剂量按1.5~2 mg/kg/天,清晨顿服,疗程6周;然后根据病情减量及巩固维持治疗)33例,年龄1~16(6.58±3.26)岁。同期选取在南京军区南京总医院体检中心常规体检的健康对照儿童122例,年龄1~14(6.24±3.32)岁。两组之间性别、年龄匹配,具有可比性。所有NS患儿和对照组儿童父母均签订知情同意书,且得到伦理委员会批准。

1.2 标本的采集与处理

急性期NS患儿血标本于激素治疗前采集;恢复期NS患儿血标本于临床激素治疗的巩固维持阶段采集;取NS患儿和对照组儿童空腹静脉血标本3.5 mL,以3500 r/min离心5 min,迅速分离血清,当天完成检测。

1.3 仪器与试剂

血清总胆固醇(TC)、三酰甘油(TG)水平测定采用英国Randox公司试剂盒;高密度脂蛋白胆固醇(HDL-C)、低密度脂蛋白胆固醇(LDL-C)水平测定采用日本第一化学株式会社试剂盒;ALB水平测定采用北京利德曼公司试剂盒;NEFA水平测定采用宁波医杰公司试剂盒;尿素、肌酐、尿酸水平测定采用四川迈克生物科技股份有限公司试剂盒,视黄醇结合蛋白4(RBP4)水平测定采用上海北加公司试剂盒,上述项目测定仪器均为日立公司Hitachi 7600全自动生化分析仪;尿N-乙酰-β-D-氨基葡萄糖苷酶(NAG)水平测定采用上海素尔生物科技有限公司试剂盒。

1.4 测定方法

NEFA测定采用酶比色法测,ALB测定采用溴甲酚绿法,TG和TC测定采用氧化酶法,HDL-C和LDL-C测定采用直接法,尿素测定采用脲酶-谷氨酸脱氢酶偶联法,肌酐测定采用肌氨酸氧化酶法,尿酸测定采用尿酸酶过氧化物酶偶联法,总蛋白测定采用双缩脲法,RBP4测定采用免疫比浊法,尿NAG酶测定采用终点法。测定前用相应校准品定标,用低、中和高值质控品进行室内质控。

1.5 统计学分析

用SPSS 20.0软件进行。正态分布数据采用均数±标准差表示,两组间比较采用两独立样本的t检验。偏态分布数据采用中位数(第25~75百分位数)表示,两组间比较采用Mann-Whitney U检验。变量间相关性采用Spearman相关分析和多元线性回归分析。以$P<0.05$为差异有统计学意义。

2 结果

2.1 NS患儿和健康对照者的血清生化指标分析

与对照组儿童相比,NS患儿血清ALB水平显著降低,NEFA水平无明显变化,而NEFA/ALB比值显著升高;此外,NS患儿血清TC、TG、LDL-C、尿酸水平及尿NAG酶水平均显著升高,HDL-C、总蛋白水平均显著降低(表1)。

2.2 急性期与恢复期NS患儿的血清生化指标分析

与恢复期NS患儿相比,急性期患儿血清ALB水平显著降低,NEFA/ALB比值显著升高;此外,急性期患儿血清TC、TG、LDL-C、尿素、肌酐、尿酸水平均显著升高,总蛋白水平显著降低(表2)。

2.3 NS患儿血清NEFA/ALB比值与其它生化指标的相关性分析

相关性分析显示,NS患儿血清NEFA/ALB比值与TC(r=0.564,P<0.001)、TG(r=0.444,P<0.001)、LDL-C(r=0.625,P<0.001)、尿素(r=0.437,P<0.001)、肌酐(r=0.278,P=0.013)、尿酸(r=0.397,P<0.001)水平均呈显著正相关;与总蛋白(r=-0.461,P<0.001)水平呈显著负相关。

进一步逐步多元线性回归分析显示,在校正其他相关因素的影响下,NS患儿血清NEFA/ALB比值与尿素水平仍呈显著独立相关(β=0.703,P=0.001;校正R^2=0.494,表3)。

3 讨论

NS由于大量ALB从尿中排出,促使肝脏代偿合成ALB增加;同时,由于肾小管摄取滤过的ALB增多,促使ALB的分解也增加;当肝脏代偿合成的蛋白增加不足以克服经肾脏的丢失和分解时,机体即会发生低蛋白血症[8]。NS患者长期慢性的低蛋白血症可进一步刺激肝脏合成各类脂质、脂蛋白增加,因此,NS患者常常伴有高脂血症[8-9]。本研究发现,儿童原发性NS患者血清ALB、总蛋白水平显著降低,而TC、TG、LDL-C水平显著升高;且急性期患儿较恢复期患儿的变化更为显著;与文献报道一致[10-11]。可见,NS患儿体内明显的低蛋白

表1 NS患儿与健康对照组血清生化指标分析

Tab.1 Serum biochemical parameters in NS children and healthy controls

Group	NS (n=88)	Controls (n=122)	t/Z	P
NEFA (mmol/L)	0.57±0.25	0.64±0.15	1.865	0.065
ALB (g/L)	22.50 (15.93-34.88)	45.55 (43.88-46.93)	11.152	<0.001
NEFA/ALB (μmol/g)	21.49 (14.47-34.25)	14.65 (11.93-15.97)	4.991	<0.001
TC (mmol/L)	8.49 (5.27-10.62)	4.09 (3.70-4.65)	10.393	<0.001
TG* (mmol/L)	2.05 (1.34-3.36)	0.83 (0.63-1.12)	10.805	<0.001
HDL-C (mmol/L)	1.77±0.46	2.23±0.67	3.165	0.002
LDL-C (mmol/L)	3.93 (2.65-5.53)	1.37 (1.18-1.54)	7.183	<0.001
Total protein (g/L)	43.50 (36.85-52.60)	70.15 (67.03-73.40)	11.477	<0.001
Urea (mmol/L)	4.20 (3.20-5.80)	4.30 (3.61-5.05)	0.229	0.819
Creatinine (μmol/L)	31.89±18.75	34.99±7.75	1.378	0.171
Uric acid* (μmol/L)	277.00 (214.25-368.25)	256.00 (204.00-291.00)	3.865	<0.001
Urinary NAG (u/gcr)	64.54±6.54	12.80±7.04	8.906	<0.001

*Data were log-transformed before analyses.

表2 NS患儿急性期与恢复期血清生化指标分析

Tab.2 Serum biochemical parameters in NS children in acute phase and in remission

Group	Acute-period (n=55)	Remission (n=33)	t/Z	P
NEFA (mmol/L)	0.55±0.25	0.62±0.24	1.447	0.152
ALB (g/L)	16.40 (14.10-21.10)	37.30 (33.75-42.15)	7.822	<0.001
NEFA/ALB (μmol/g)	26.95 (18.82-44.51)	15.59 (12.61-20.70)	4.689	<0.001
TC (mmol/L)	10.00 (8.59-12.11)	5.19 (4.59-6.33)	6.6935	<0.001
TG* (mmol/L)	2.68 (1.72-4.21)	1.34 (0.81-1.80)	5.608	<0.001
HDL-C (mmol/L)	1.84±0.48	1.71±0.47	0.655	0.519
LDL-C (mmol/L)	5.53 (4.09-6.55)	2.72 (2.04-3.67)	3.664	<0.001
Total protein (g/L)	37.90 (35.20-43.50)	56.00 (51.53-62.43)	6.851	<0.001
Urea (mmol/L)	4.90 (3.70-9.90)	1.17 (2.60-3.88)	4.676	<0.001
Creatinine (μmol/L)	35.00±21.33	26.62±11.73	2.242	0.028
Uric acid* (μmol/L)	298.00 (233.00-434.00)	261 (207.50-309.00)	3.196	0.002
Urinary NAG (u/gcr)	80.48±7.07	53.31±4.02	2.166	0.038

*Data were log-transformed before analyses.

血症、高脂血症与疾病的发生发展密切相关。

NEFA是脂肪分解代谢的产物，生理状态下处于较低水平，其在血循环中运输时，主要与ALB结合，并由此从肾小球滤出被近曲小管重吸收[12-13]。有研究表明[14]，血循环中高水平的NEFA可刺激细胞内活性氧的增加，引起内皮细胞的通透性升高，促进肾小管损伤。本研究显示，NS患儿血清NEFA水平无明显变化，这可能源于NS患儿严重蛋白尿，致使大部分与ALB结合的NEFA经肾脏丢失，导致体内NEFA含量相对降低所致。但本研究中NS患儿血清NEFA/ALB比值却显著升高，由此推测NS患儿体内ALB的下降较NEFA的水平变化更为明显，NEFA/ALB比值分析较单纯的检测NEFA水平更有价值，更能反映患儿体内NEFA、ALB的相对水平。当体内NEFA水平病理性增高时，与ALB结合的NEFA可先通过肾小球过滤再重吸收至近端小管，从而对肾小管上皮细胞产生脂毒性作用，促使其凋亡增加及功能受损[15-19]；在伴蛋白尿的慢性肾病中，NEFA与ALB的复合物被肾小管重吸收后，可引起体内脂质的积聚过多及脂肪酸β氧化的异常，致使脂肪酸的代谢去路障碍，进一步促进肾脏疾病的发生发展[20-21]。可见，与ALB结合的NEFA是导致肾小管损伤的重要因素。本研究相关性分析显示，NS患儿血清NEFA/ALB比值与各肾功能参数均显著相关；进一步多元线性回归分析显示，血清尿素水平可作为NEFA/ALB比值的独立预测因子，提示NEFA/ALB比值的升高与NS患儿的肾功能损伤的关系密切。为进一步探讨NEFA/ALB比值的临床意

表3 多元线性回归分析各因素对NS患儿血清NEFA/ALB比值的影响

Tab.3 Multiple linear regression analysis of factors affecting serum NEFA to ALB ratio in NS children

	Unstandardized coefficients		Standardized coefficient	*P*
	B	SE	Beta	
Independent variables in the model				
Constant	9.363	4.183		0.038
Urea	2.934	0.701	0.703	0.001
Independent variables excluded from the model				
TC	-	-	0.210	0.381
TG	-	-	0.124	0.492
HDL-C	-	-	-0.045	0.796
LDL-C	-	-	0.212	0.369
Creatinine	-	-	0.056	0.863
Uric acid	-	-	-0.139	0.665

The dependent variable is serum NEFA to ALB ratio (adjusted R^2=0.494).

义及应用价值，本结果还显示，急性期患儿血清NEFA/ALB比值显著高于恢复期患儿，且较其他常规肾功能参数、血脂指标的变化更为明显，提示NEFA/ALB比值也有助于NS患儿的病情评估。

综上所述，儿童NS患者血清NEFA/ALB比值显著升高，与肾功能损伤密切相关；急性期NS患儿血清NEFA/ALB比值显著高于恢复期患儿，NEFA/ALB比值有助于NS患儿的病情评估。

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（编辑：吴锦雅）